

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

REMARKS

Claims 1-15 are pending in the present application.

Claims 1 and 14 provide, in part, a novel crystal form of N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine methyl ester (Neotame), which exhibits a characteristic X-ray diffraction peak at a diffraction angle, 2θ , measured using a $\text{CuK}\alpha$ rays of about 7.1° (referred to hereinafter as "C-type crystals" or the "C-type crystal form").

Present Claim 2 relates to a process for producing such crystals. Present Claims 3, 4, and 15 relate to granules which contain C-type crystals of Neotame, and present Claims 5-13 relate to compositions which contain C-type crystals of Neotame.

The C-type crystals of the present claims are distinct from the A-type crystals afforded by one of the cited references (i.e., Nofre et al). Moreover, the inventors have surprisingly found that the presently claimed crystals exhibit an increased rate of dissolution in water, as compared to A-type crystals, even though the C-type crystals contain less water than the A-type crystals. Further, none of the art of record, individually or in combination, provide reasonable guidance to lead the artisan to (a) foresee the presence of the C-type crystals of Neotame, (b) foresee the advantageous properties flowing from the C-type crystals of Neotame, or (c) provide any guidance as to how one of skill in the art would obtain the C-type crystals of Neotame. Accordingly, the art of record, individually or in combination, cannot affect the patentability of the present claims.

Reconsideration is requested in view of the following comments.

The rejection of Claims 1-15 under 35 U.S.C. § 103 (a) in view of U.S. patent No. 4,810,818 (Wakamatsu et al) in further view of U.S. Patent No. 5,480,668 (Nofre et al) is traversed.

As conceded on page 3 of the Official Action dated May 31, 2002 (paper number 15), Wakamatsu et al is concerned only with Aspartame and is completely silent in regard to Neotame. Nofre et al discloses certain derivatives of Aspartame, including Neotame. However, there is no teaching in Nofre et al of the presently claimed C-type crystals. In fact, as shown in the Declaration of Nagashima filed on September 21, 2001, the Neotame produced according to Nofre et al exists in either an amorphous state or as A-type crystals.

On November 19, 2002, Applicants filed the Declaration of Kashiwagi (a copy of which is enclosed herewith for the Examiner's convenience), which stated that polymorph or pseudo-polymorph related crystal forms exhibit different physical properties that can have a large influence on the industrial processing of the compound (see paragraph 5). Moreover, the discovery of a new crystal form of a known compound not only is unexpected but also can be commercially important. In fact, no prior art reference has been cited which stands for the proposition that the mere existence of one crystal form for a given compound would suggest the existence of another, different crystal form for that compound (a fact conceded by the Examiner at page 5, paragraph (e) of paper number 22).

Despite this showing, the Examiner attempts to support this ground of rejection, by dismissing the Declaration of Kashiwagi as "not persuasive." Specifically, in paragraph (d) on page 5 of paper number 22, the Examiner disregards the argument that the different crystalline forms exhibit different physical properties, which have a large influence on the industrial processing thereof. Additionally, the Examiner disregards the argument that the discovery of a new crystal form of a known compound is unexpected.

The basis for the Examiner's conclusion is that Wakamatsu et al disclose a method of producing a more soluble crystalline form of aspartame by drying the aspartame to a water content of 2.6% by weight (page 3, lines 1-3 of paper number 22). The Examiner states that the ability to obtain more soluble crystalline forms of aspartame by reducing the water content would "motivate one of skill in the art to do the same with neotame." To support this assertion the Examiner states that the motivation is derived from the "close structural similarity" and the overlap in chemical and physiological behaviors between aspartame and Neotame. The Examiner also asserts that there would be a reasonable expectation that the same result would hold true for Neotame as was determined for aspartame.

However, Applicants disagree with these assertions by the Examiner. In fact, Applicants note that the Examiner has elected to disregard the conceded deficiencies in the disclosures of Wakamatsu et al and Nofre et al (i.e., that no prior art reference has been cited which stands for the proposition that the mere existence of one crystal form for a given compound would suggest the existence of another, different crystal form for that compound." In paragraph (e) on page 5 of paper number 22, the Examiner states that "this point is not at issue in the rejection of record" since his rejection is based on the "fact" that the structural similarities would motivate the artisan to employ the process of Wakamatsu et al to Neotame. However, this latter assertion by the Examiner is contradictory to the former. In fact, as Applicants have clearly demonstrated in the Declaration of Kashiwagi, the discovery of a new crystal form of a known compound not only is unexpected but also can be commercially important (see paragraph 5). Accordingly, it appears that the Examiner is mistaking motivation to experiment for the requisite expectation of success.

Further, the Examiner appears to be using impermissible hindsight in an effort to support the proposition that Neotame *may* have a more soluble crystalline form at reduced

water concentrations. Moreover, the Examiner has not provided any reference to support his position that there would be a “reasonable expectation” of any alternate crystal form of Neotame. Seemingly in support of the Examiner’s belief, the Examiner states that “Wakamatsu teaches one of ordinary skill in the art to expect that the analogs of Aspartame (of which Neotame is one) may be expected to exhibit different crystalline forms depending upon water content” (paragraph (d) on page 5 of paper number 22). However, this assertion by the Examiner is without merit as Wakamatsu et al does not explicitly teach this correlation and the Examiner is merely inserting his own opinions under the guise of Wakamatsu et al. Applicants submit herewith a copy of Ex parte Jones, 62 USPQ2d 1206 (BdPatApp&Int 2001), which states that when an Examiner maintains that there is an implicit teaching or suggestion in the art, “the Examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art.” Therefore, this assertion by the Examiner does not meet the burden necessary to establish a *prima facie* case of obviousness.

Further, the Examiner asserts “Wakamatsu provides both the process for obtaining Applicant’s crystalline form and the motivation to apply it neotame” (see paragraph (e) in the paragraph bridging pages 5 and 6 of paper number 22). To support this assertion the Examiner cites In re Grose and Flanigen, 201 USPQ 57 (CCPA 1979). However, In re Grose and Flanigen does not support the Examiner’s position. This decision merely states that any differences in diffraction data must be significant to establish that two crystals are truly different crystal forms. The Declaration of Kashiwagi submitted on November 19, 2002 has clearly met this burden. Therefore, Applicants once again submit that, even if there were a *prima facie* case of obviousness, Applicants *have met* their burden to rebut the obviousness rejection.

Moreover, Applicants submit herewith In re Certain Crystalline Cefadroxil Monohydrate, 15 USPQ2d 1263 (US ITC 1990) and In re Cofer, 148 USPQ 268 (CCPA 1966), which are part of a long-held precedent that a new crystalline form of a compound is *not* obvious absent evidence that “the prior art suggests the *particular structure or form* of the compound or composition *as well as* suitable methods for obtaining that structure or form.” In other words, a crystalline chemical compound is not obvious unless its structure and methods for obtaining that structure are obvious. Applicants submit that the Examiner has not provided any reference or evidence to support the notion that the *structure* of the C-type crystal form of Neotame would be obvious. In fact, at paragraph 11 and Figure 3 of the Declaration of Kashiwagi show that Neotame has, at least, 4 crystal types labeled A-type, C-type, D-type, and E-type, none of which are disclosed or suggested by Wakamatsu et al and/or Nofre et al. Therefore, contrary to the Examiner’s assertions, Applicants submit that it is not possible to predict crystals structures and/or properties of crystals based solely on structural similarity as the Examiner alleges. In fact, the Examiner concedes that no prior art reference has been cited which stands for the proposition that the mere existence of one crystal form for a given compound would suggest the existence of another, different crystal form for that compound, much less any other compound (see page 5, paragraph (e) of paper number 22). Accordingly, the Examiner has failed to make out a *prima facie* case of obviousness with respect to any expectation that the C-type crystals of Neotame would have “a characteristic X-ray diffraction peak at a diffraction angle, 2θ , measured using a $\text{CuK}\alpha$ ray, of about 7.1° ” (see Claim 1).

Wakamatsu et al exclusively relates to Aspartame crystals, and only discloses a method for reducing II-type crystals formation by prevention of overdrying. According to the descriptions presented in this reference, the Aspartame is dried at a high temperature (70°C or

higher) when the water content is 5-15% to give the II-type crystals. Wakamatsu et al also disclose that it is possible to prevent the II-type crystals formation when the Aspartame is dried below this water content at a low temperature (50°C or lower). In other words, Wakamatsu et al provide the following 2 processes:

1) When Aspartame crystals are dried at the high temperature under a usual condition, Aspartame dried crystals of I-type and II-type containing the II-type crystals thereof in a high ratio are produced; and

2) A transfer (conversion) of I-type crystals into II-type crystals is produced under a range of water content 5-15%. Therefore, they are dried at the low temperature under the water content 5-15%, so as to minimize the formation of II-type crystals.

In case 1), the Aspartame crystals before drying are I-type crystals (accurately, IA-type crystals). In addition, the drying *at a high temperature* is employed in view of drying efficiency.

As described clearly in Wakamatsu et al (column 1, lines 48 and 49), the I-type crystals of Aspartame possess superior solubility properties compared to the II-type crystals. Accordingly, the I-type crystals with a high water content (IA-type crystals: 6% or higher; IB-type crystals: 2-6% or so) are dried to produce the II-type crystals with a lower water content (IIA-type crystals: 0.9-3% or so; II-type crystals: 0.9% or lower). The I-type crystals with the higher water content have an excellent solubility, and in contrast, the II-type crystals with a water content of 3% or lower have a poor solubility. Applicants submit herewith, U.S. 4,579,747 (Sugiyama et al), column 3, lines 19-27, which provides support for the accurate characterization of Aspartame crystal forms and the water content thereof.

For the Examiner's convenience, Applicants submit the following summary of the Aspartame crystals provided by Wakamatsu et al (and further supported by Sugiyama et al):

[Crystal Forms]

I A-type (wet crystals) ↔ I B-type (dry crystals; water content: 2-6% or so)
 ↓ drying
II B-type crystals ↔ II A-type (dry crystals; water content: 3% or less)

As can be seen above, further drying the II A-type crystals can produce the II B-type crystals.

With reference to the relative solubilities and the corresponding correlation to the water content of the various Aspartame crystalline forms, Applicants provide the following (taken from Wakamatsu et al and Sugiyama et al):

[Solubility]

I A-type > I B-type > II A-type > II B-type
 ← better; worse →

[Water Content]

I A-type > I B-type > II A-type > II B-type
 ← higher; lower →

In view of the foregoing, the solubility Aspartame crystals improve in proportion to the water content contained therein. As the Aspartame crystals are dried to reduce the water content the solubility thereof is correspondingly reduced.

In contrast, in the present invention, as shown in Example 1 (see page 9), the C-type crystals of Neotame (water content: 0.8%) are obtained by drying the A-type crystals (water content: 5%). However, the solubility of the C-type crystals are significantly improved compared to that of the A-type crystals, even though the water content in the C-type crystals

is lower than that in the A-type crystals. The present invention can be summarized as follows:

[Crystal Forms/Neotame]

A-type crystals drying
 → C-type crystals

[Solubility]

A-type < C-type

[Water Content]

A-type > C-type

Accordingly, Applicants submit that if the artisan were to attempt to extrapolate the disclosure of Wakamatsu et al to the Neotame as alleged by the Examiner, based on the state of the art gleaned from the disclosures of Wakamatsu et al and Sugiyama et al, it may be surmised that the A-type Neotame crystals are more soluble than the C-type Neotame crystals. However, contrary to such a supposition, just the opposite has been discovered in the present invention.

For all the foregoing reasons, Applicants submit that Wakamatsu et al and Nofre et al fail to render the present invention obvious. Applicants request withdrawal of this ground of rejection and allowance of all claims in the present application.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Vincent K. Shier, Ph.D.
Registration No. 50,552



22850

(703) 413-3000
Fax #: (703) 413-2220
NFO/VKS